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EXAMINER
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ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
04/28/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/579,769	STAEHLER ET AL.	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 13, 2009 is acknowledged. Claims 1, 2, 20, 21 and 26-31 (currently amended), claims 3-19 and 22-25 (original or previously presented) and claims 32 and 33 (newly added) will be examined on the merits.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Chetverin et al. (U.S. Patent No. 6,322,971).

Chetverin teaches a method for preparing a plurality of different synthetic single-stranded nucleic acids (sectioned arrays are used to sort and hybridize different nucleic acid strands to oligonucleotides at different areas and amplify the different nucleic acids in parallel, column 4, lines 5-20), comprising the steps:

(a) providing a support with a surface which comprises a plurality of positions at each of which different nucleic acid fragments are present, comprising base sequences which are complementary to the nucleic acids to be prepared (the sorting arrays contain oligonucleotides comprising constant and variable segments that are complementary to a region within the target sequence to allow hybridization, column 16, lines 31-40 and Figure 4B, third step),

(b) adding nucleotide building blocks and an enzyme which brings about generation of different single-stranded nucleic acids from the complementary base sequences from (a) (the array is incubated with a DNA polymerase to produce a complementary single-stranded copy of each hybridized strand by extension of the 3' end of the oligonucleotides bound to the array, column 16, lines 40-44 and Figure 4B, step 4), and

(c) detaching the nucleic acids generated in step (b) and, where appropriate, providing for further operations (further amplification of the extension products, such as by PCR, see Figure 4B, last step, allows the reaction to proceed both on the surface and in solution, and the products in solution, which represent both strands of the duplex, can then be transferred to a separate array to produce replicate arrays, column 4, lines 9-13 and 20-24 and column 10, line 66 to column 11, line 4; amplified DNA molecules produced on an array can be transferred, such as in a blotting procedure, from a partial array onto a mirror copy of the array, after melting the strands free from the other partial strand, column 73, lines 26-30; isolated strands from an array can also be inserted into vectors for cloning, or further amplified for sequencing, column 22, lines 26-29).

With regard to claim 2, Chetverin teaches a method for preparing a predetermined nucleic acid double strand (sectioned arrays are used to sort and hybridize different nucleic acid strands to different areas and amplify the different nucleic acids in parallel to produce double-stranded products, column 4, lines 5-20 and Figure 4B, step 4), comprising the steps:

(a) providing a support with a surface which comprises a plurality of positions at each of which different nucleic acid fragments are present, comprising base sequences which are complementary to partial sequences of the nucleic acid double strand to be prepared (the sorting arrays contain oligonucleotides comprising constant and variable segments that are complementary to a region within the target sequence to allow hybridization, column 16, lines 31-40 and Figure 4B, third step),

(b) adding nucleotide building blocks and an enzyme which brings about generation of single-stranded partial sequences of the nucleic acid double strand to be prepared from the complementary base sequences from (a) (the array is incubated with a DNA polymerase to produce a complementary copy of each hybridized strand by extension of the 3' end of the oligonucleotide bound to the array, column 16, lines 40-44 and Figure 4B, step 4; partial sequences are prepared when internal target sequences are bound to the array, column 4, lines 44-47 and Figure 5B), and

(c) assembling the single-stranded partial sequences generated in step b) to give the desired nucleic acid double strand (based on examination of overlapping terminal nucleotides of partial sequences, sequence blocks are first assembled and then ordered to determine the full sequence, column 6, lines 9-29, column 36, line 34 to column 37, line 44 and Figure 9A and 10A-C; sequences can also be covalently assembled together by ligation using an immobilized splint oligonucleotide, column 79, lines 54-60).

With regard to claims 3 and 4, Chetverin teaches a method characterized in that the support is selected from flat supports, porous supports, reaction supports with electrodes, reaction supports with particles or beads, microfluidic reaction supports

which optionally have surface modifications such as gels, linkers, spacers, polymers, amorphous layers or/and 3D matrices, and combinations of the aforementioned supports (support is first prepared as a flat sheet or plain array, and then is converted by surface modifications into a sectional array by making physical depressions in a deformable solid support to isolate the areas in each depression to allow fluidic reactions to remain isolated from each other, column 4, lines 5-13, column 10, lines 14-26 and Figure 2 and 2A).

With regard to claim 5, Chetverin teaches a method characterized in that the nucleic acid fragments from (a) are generated by spatially resolved in situ synthesis on the support (reactions occurring in different wells of the array are highly specific based on the immobilized oligonucleotide in each well to allow a large number of separate amplification reactions to be performed in parallel, column 4, lines 13-16).

With regard to claims 6 and 7, Chetverin teaches a method characterized in that the nucleic acid fragments from (a) are synthesized by spatially or/and time-resolved illumination by means of a programmable light source matrix within the chambers of one or more reaction zones within a fluidic reaction chamber (immobilized fragments can be synthesized within the wells of a sectioned array by automated photolithography techniques such as light-directed spatially addressable parallel chemical synthesis, column 13, line 57 to column 14, line 3 and column 33, lines 26-30).

With regard to claim 8, Chetverin teaches a method characterized in that the assembly of the partial sequences in step (c) takes place at least partly in one or more

steps on the support (sequences can be assembled together by ligation using an immobilized splint oligonucleotide as a template, column 79, lines 54-60).

With regard to claim 9, Chetverin teaches a method characterized in that the nucleic acid fragments from (a) are chosen so that the nucleic acids or partial sequences formed in step (b) can be joined to give nucleic acid double-stranded hybrids (oligonucletides immobilized to the support allow synthesis of a complete set of partial sequences of the nucleic acid of interest, which can then be ordered into a full sequence, column 6, lines 9-18).

With regard to claims 10 and 11, Chetverin teaches a method characterized in that a plurality of nucleic acids or partial sequences which form a strand of the nucleic acid double strand are covalently connected together comprising a treatment with ligase (sequences can be covalently assembled together by ligation using an immobilized splint oligonucleotide as a template, column 79, lines 54-60).

With regard to claim 12, Chetverin teaches a method characterized in that step (b) comprises the addition of at least one primer for each position of the support, the primer being complementary to part of the nucleic acid fragment located at this position and step (b) comprising an elongation of the primer (linear amplification of the hybridized strand is primed by the 3' end of the immobilized oligonucleotide and universal PCR primers are added, with extension of these primers resulting in PCR amplification of the sequence, column 16, lines 39-41 and 47-52 and Figure 4B, bottom).

With regard to claim 13, Chetverin teaches a method characterized in that double-stranded nucleic acid fragments are provided in step (a), with at least one strand being tethered to the surface of the support (masking oligonucleotides can be hybridized to the immobilized oligonucleotide prior to addition of the target strand, column 12, lines 19-26).

With regard to claim 14, Chetverin teaches a method characterized in that step (b) comprises transcription of double-stranded DNA fragments or/and replication of double-stranded RNA fragments (transcription reactions can be carried out in the wells of a sectioned array if the immobilized oligonucleotide contains a promoter sequence, column 9, lines 56-60 and column 27, lines 55-60).

With regard to claims 15 and 17, Chetverin teaches a method characterized in that nucleic acid fragments or double-stranded, circular fragments comprising a self-priming 3' end are provided in step (a), and step (b) comprises elongation of the 3' end (some sequences of fragments formed on the array may contain perfect repeats that fold back on itself to serve as self-overlapping termini, which would naturally include the formation of circular type molecules, and thus can lead to extension using the same fragment as a template and thus compromise the ability to order sequence blocks, column 38, lines 26-41).

With regard to claims 16 and 18, Chetverin teaches a method which comprises elimination of the elongation product (formation of such ambiguities can be drastically reduced by using longer probes in such recursive sequence regions, and using larger

amounts of all variable oligonucleotides on the array, column 38, line 58 to column 39, line 3).

With regard to claim 19, Chetverin teaches a method characterized in that the nucleic acid fragments from (a) are generated by:

- provision of capture probes at the positions (arrays comprise immobilized oligonucleotides complementary to the target sequences in order to bind the target strands at fixed locations in the array, column 3, lines 46-54 and column 8, lines 46-51) and

- binding of nucleic acid fragments from a fluid passed over the support to the capture probes (solutions are spread across the arrays containing the immobilized oligonucleotides, and include restriction digests of DNA samples added to the array after melting the strands, column 14, lines 53-54, column 16, lines 23-31 and Figure 5, first step), where the capture probes are complementary to partial regions of the nucleic acid fragments (the immobilized oligonucleotides are complementary to the variable and constant regions of the target strands, including internal sequences that allow partial products to be synthesized, column 5, lines 25-37, column 16, lines 32-38 and Figure 5, second step).

With regard to claims 20 and 32, Chetverin teaches a method wherein recognition sequences for specific interaction with molecules such as proteins, nucleic acids, peptides, drugs, saccharides, lipids, hormones or/and organic compounds are present at one or more positions in the sequence of the generated nucleic acids (the constant regions of the immobilized oligonucleotides can contain priming or transcription

promoter sites that interact with primers through hybridization and polymerases that bind to the priming or promoter sites, column 9, lines 57-60 and column 27, lines 57-60).

With regard to claims 21 and 33, Chetverin teaches a method wherein the sequence of the generated nucleic acids is a naturally occurring sequence, a non-naturally occurring sequence or a combination thereof (the immobilized oligonucleotides are synthetic nucleic acids made directly on the support or attached to the support after synthesis, and contain sequences complementary to natural sequences present in the sample nucleic acids, column 12, line 41 to column 13, line 3, column 13, lines 4-31 and column 16, lines 31-36; the nucleic fragments can comprise a strand from a melted restriction fragment obtained from a DNA sample, column 16, lines 22-36).

With regard to claim 22, Chetverin teaches a method characterized in that the sequence is taken from a database, from a sequencing experiment or from an apparatus for integrated synthesis and analysis of polymers (arrays can be synthesized by an automated process, column 13, lines 32-47, and can comprise constant region sequences common to all probes and variable region sequences that are complementary to different sequences of the target, column 9, lines 20-33 and Figure 1A).

With regard to claim 23, Chetverin teaches a method characterized in that the nucleotide building blocks may comprise naturally occurring nucleotides, modified nucleotides or mixtures thereof (immobilized oligonucleotides bound to nucleic acid templates are extended using an appropriate DNA polymerase and nucleotides, column

29, lines 32-34; extension can also be performed by only one nucleotide using dideoxynucleotides as substrates for the DNA polymerase, column 29, lines 34-39).

With regard to claims 24 and 25, Chetverin teaches a method characterized in that modified nucleotide building blocks are used for labeling and subsequent detection of the nucleic acids or of the joined nucleic acid double strands in a light-dependent or/and electrochemical manner (the dideoxynucleotides used in extension reactions can be tagged with different labels such as fluorescent dyes to provide for detection by scanning the arrays at different wavelengths, column 29, lines 41-49).

With regard to claims 26 and 27, Chetverin teaches a method wherein said prepared nucleic acids are tools for therapeutic, pharmacological or diagnostic purposes (the method is useful for surveys of selected oligonucleotides for clinical diagnostic procedures, column 7, lines 12-16; RNA copies can be produced from RNA polymerase promoter sequences introduced in primer sequences, which could be used for anitsense or miRNA applications, column 69, lines 22-27).

With regard to claim 28, Chetverin teaches a method further comprising transferring said prepared nucleic acids into effector cells (isolated sequences from an array can be inserted into vectors for cloning and transformation of microbial cells, column 22, lines 26-29 and column 2, lines 54-57).

With regard to claims 29 and 30, Chetverin teaches a method wherein said prepared nucleic acids are stabilized, condensed or/and topologically manipulated during a stepwise combination and joining or subsequent thereto, wherein the stabilization, condensation or/and topological manipulation is effected by functional

molecules such as histones or topoisomerases (isolated sequences from an array can also be inserted into vectors for cloning, which upon transformation into microbial cells, will undergo natural condensation and topological manipulations *in vivo*, column 22, lines 26-29 and column 2, lines 54-57).

With regard to claim 31, Chetverin teaches a method wherein said prepared nucleic acids are propagatable cloning vectors (isolated sequences from an array can also be inserted into vectors for cloning, column 22, lines 26-29; transcription sites can be placed adjacent to target sequences using primers containing promoters for amplification, column 9, lines 57-60).

Response to Arguments

4. Applicant's arguments filed February 13, 2009 have been fully considered but they are not persuasive.

Applicant has amended claims 26-31 as "method" claims and therefore the rejection of these claims under 35 USC § 101 as being non-statutory "use" claims has been withdrawn. Applicant has also amended claims 20 and 21 to correct for insufficient antecedent basis in the base claim, and therefore the rejection of these claims under 35 USC § 112, second paragraph has been withdrawn.

Applicant then argues that the 35 USC § 102 rejection of claims 1-31 over Chetverin et al. (U.S. Patent No. 6,322,971) should be withdrawn since the cited reference fails to disclose all the limitations of the claims as amended. In particular, with regard to independent claim 1, Applicant argues that Chetverin is directed to

methods of producing a copy of an unknown DNA sequence following hybridization of DNA fragments containing artificial priming sequences to the ends of the fragments to allow primer extension using the unknown sample nucleic acid as the template, whereas the instant invention is characterized as a method for the production of synthetic single- or double-stranded nucleic acids de novo on a support, wherein the extended fragments are detached from the support, and wherein the complete identity of the product is defined or known prior to beginning the method steps since the sequences on the support are complementary to the nucleic acids being prepared. The Examiner asserts that Chetverin does indeed teach all the limitations of claim 1 as amended. There is no express requirement of claim 1 that the products to be prepared be known sequences, only that the support comprise a plurality of base sequences complementary to the products. Therefore, the templates that hybridize to the bound sequences need be known only for the purpose of hybridizing to a binding site, and thus a sequence such as an adaptor may be added to the template to provide the binding site. There is also no requirement that the synthesis occur in a de novo fashion, only that nucleotide building blocks be added to bring about generation of different nucleic acid products, as is taught by Chetverin since a plurality of primer extension products are generated throughout the array. Furthermore, the products generated at step (b) are continually recycled during the amplification steps of PCR that take place both on the surface and in solution (Chetverin, column 4, lines 9-13).

Applicant then argues that Chetverin fails to disclose all the limitations of independent claim 2. In particular, Applicant argues that Chetverin only teaches a

method for preparing copies of an unknown sequence, not a predetermined nucleic acid double-stranded sequence. The Examiner asserts that each of the steps of claim 2 are expressly taught by Chetverin, including providing a support containing an array of different nucleic acid fragments (see Figure 5A) that are complementary to regions of a target nucleic acid to be prepared and serve as primers (Figure 5B, first step), extension of the primers to form partial sequences (Figure 5B, second step) and assembling of the partial sequences to form double-stranded products by various methods, including assembly by overlapping of partial sequences (column 6, lines 9-29, column 36, line 34 to column 37, line 44 and Figures 9A and 10A-C), and covalent assembly of partial sequences by ligation using splint oligonucleotides, column 79, lines 54-60), the product of which can then be converted to double-stranded products by PCR amplification (column 80, lines 7-9). Thus, the partial sequences that are prepared are "predetermined" because they are recognized by primers bound to the support and produce a series of partial products that can be arranged into a full-length product. Therefore, for all the reasons stated above, the 102 rejection of claims 1-31 and newly added claims 32 and 33 over Chetverin is maintained.

Summary

5. Claims 1-33 are rejected. No claims are allowable.

Conclusion

6. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637